

Non-Linear Dynamics in Patients with Stable Angina Pectoris ¹

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Abstract

Dynamic analysis techniques may quantify abnormalities in heart rate behaviour based on non-linear and fractal analysis. The applicability of these new methods for detecting complex heart rate dynamics in coronary heart disease is not well established. To investigate the clinical and prognostic significance of fractal dimension and detrended fluctuation analysis, two different groups were studied, group of patients with stable angina pectoris without previous myocardial infarction, and age-matched healthy controls. The fractal dimension of the RR series was determined using the rescaled range (R/S) analysis technique. To quantify fractal long-range-correlation properties of heart rate variability, the detrended fluctuation analysis (DFA) technique was used. The heart rate variability was characterized by a scaling exponent α , separately for short-term (< 11 beats) and for long-term (> 11 beats) time scales. The results of data sets show the existence of crossover phenomena between short-time scales. In patients with stable angina pectoris the short-term fractal scaling exponent (α_1) was significantly lower (0.95 ± 0.05 vs. 1.08 ± 0.06 ; $p < 0.05$), while there were no differences in the long-term fractal scaling exponent (α_2) (1.37 ± 0.26 vs. 1.39 ± 0.04 ; $p < 0.05$). The patients with stable angina pectoris also had higher fractal dimension than a healthy control group ($p < 0.05$). The short-time scaling exponent and fractal dimension are better than other heart rate variability parameters in differentiating patients with stable angina pectoris from healthy subjects. Dynamic analysis may thus complement traditional analysis in detecting altered heart rate behaviour.

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1 Introduction

Heart rate variability (HRV) [1, 2] reflects the modulation of the cardiac function by autonomic and other physiological systems, and its measurements from ambulatory electrocardiography (ECG) recordings during an exercise ECG test may be a useful method for both clinical and scientific purposes.

Traditional linear statistical measures provide limited information about HRV, because non-linear mechanisms may also be involved in the genesis of HR dynamics. A number of new methods have recently been developed to quantify complex heart rate dynamics. They may uncover abnormalities in the time series data, which are not apparent when using conventional linear statistical methods. This study tested the hypothesis that fractal measurements of HRV are altered in patients with stable angina pectoris [3, 4].

2 Methods

2.1 Patients

Twenty five consecutive patients with stable angina pectoris and without previous myocardial infarction were included in the analysis after the history of chest pain and non-invasive cardiovascular diagnostic measurements (ECG at rest, echocardiography, 24 hours ECG, vectorcardiography, exercise ECG test and laboratory coronary risk factors measurements) with ECG evidence of ischemic STsegment depression (> 0.1 mV) during an exercise test. They were 57 ± 6 years old, 12 male. No cardiac medication was allowed on the day of testing, and β -blocking therapy was withdrawn at least 7 days before and calcium antagonists at least 2 days before. Patients with anginal chest pain, silent ischemic ST-segment depression during the 24 hour ECG recording and diabetes mellitus were excluded. The control group consisted of 20 randomly selected age matched (mean age 58 ± 8 years), and sex matched (11 male) healthy subjects. After a complete non-invasive examination and their medical history all patients revealed no cardiovascular disease or use of medication. All controls had normal ECG at rest, echocardiographic data (M-mode, 2D dimensional and Doppler echocardiography), normal arterial blood pressure and fasting blood glucose. Subjects with evidence of ischemic ST-segment depression during the exercise ECG test or the 24 hour ECG recording were not included. An exercise ECG on all subjects was obtained using a symptom or ECG changes limited

test, increasing the workload in a controlled manner. A horizontal or downsloping ST-segment depression of > 0.1 mV occurring 0.08 seconds after the J point was considered to be of ischemic origin.

2.2 Analysis of HRV

Series of RR intervals were obtained from high resolution ECG (sampling frequency 1000 Hz), and the recording time scale during the exercise ECG test was approximately about 1500 beats. The ECG data were digitized by the Vawebok 512 (Iotech. Cal. USA), and transferred to a computer for analysis. The RR interval series was passed through a filter that eliminated noise, artifacts and premature beats. All RR interval series were first edited automatically, after which careful manual editing was performed by visual inspection of each RR interval. After this, all questionable portions were excluded manually, and only segments with $> 85\%$ sinus beats were included in the final analysis.

The fractal dimension of the RR interval series was determined by the "Rescaled range" (R/S) analysis [5]: $R(n)/S(n) \sim n^H$, where H is the Hurst's exponent, an important parameter used to characterize the time series. $H \sim \log(R/S)/\log(n)$ where n is the length of the time box.

If the Hurst exponent is approximately about 0.5, it represents an ordinary random walk or Brownian motion. In the cases where H is < 0.5 , it means negative correlation between the increments (antipersistent time series) and if it is > 0.5 , it means positive correlation between the increments (persistent time series which are plentiful in nature).

The Hurst exponent is related to the fractal dimension (FD): $H = E + 1 + FD$, where E is the Euclidean dimension ($E = 0$ for point, 1 for line and 2 for surface). The relation between H and FD of the graph of a random fractal is $FD = 2H$ for one dimensional signal. While H vary from 0 to 1, FD decreases from 2 to 1.

The Hurst's exponent as well as the fractal dimension were determined for the whole time series during the exercise ECG, and also separately for each program of exercise including half a minute baseline ECG before the exercise and six minutes of relaxation after the exercise (Figs.1 and 2).

To quantify fractal long-range correlation properties of HRV, the detrended fluctuation analysis (DFA) technique [6], which is a modified root-mean-square (rms) analysis of a random walk, was used. The method quantifies the presence or absence of fractal long-range correlation properties. The rms fluctuation of

integrated and detrended time series is calculated by the formula

$$F(n) = \sqrt{\frac{1}{N} \sum_{k=1}^N [y(k) - y_n(k)]^2} ,$$

where

$$y(k) = \sum_{i=1}^k (R(i) - \bar{R})$$

and $y_n(k)$ is the regression line through the data $y(i)$ in the box of length n . This computation is repeated over all time scales (box sizes n) in order to characterize the relationship between $F(n)$, the average fluctuation, as a function of box size. Typically, $F(n)$ will increase with box size n . A linear relationship in a log-log plot indicates the presence of power law (fractal) scaling. In this study, HRV was characterized by a scaling exponent α , the slope of the linear relationship between $\log F(n)$ and $\log n$, separately for short-term (< 11 beats, α_1), and long-term (> 11 beats, α_2) fluctuations in the RR series data (Fig.3).

2.3 Statistical analysis

Results are expressed as mean \pm standard deviation (SD). The p value < 0.05 was considered significant.

3 Results

The baseline clinical and heart rate variables of healthy controls and patients with stable angina pectoris are listed in Table 1. There were no differences observed in conventional statistical linear measures of the HRV (average RR intervals and SDNN in the time domain and LF/HF ratio in frequent domain). The results of exercise data sets show the existence of crossover phenomena between short-time scales when using the DFA method. A significant difference was found between patients with stable angina pectoris and healthy controls in short-time scales (0.95 ± 0.05 vs. 1.08 ± 0.06) as can be seen in Figure 3. However there were no significant differences in long-term series. The fractal dimension was significantly higher in patients with stable angina pectoris.

The main findings of this study are compared with healthy controls. Because of a relatively small patient population, the results of this study do not allow us to draw conclusions regarding the lack of the prognostic value of HRV in

Clinical data (n=45):	Healthy Controls (n=20)	Patients with SAP (n= 25)
Age (yrs)	58 \pm 8	57 \pm 6
Men/women	11/9	12/13
ECG at rest (freq.)	74	81
VPCs/hour	3 \pm 0.7	4 \pm 2.7
LV ejection fraction(%)	71 \pm 6	63 \pm 9
E/A wave	1.4 \pm 0.2	0.8 \pm 0.2
Exercise ECG data:		
Average RR interval (ms)	874 \pm 108	856 \pm 114
SDNN (ms)	149 \pm 41	139 \pm 40
LF/HF ratio	3.2 \pm 1.5	3.5 \pm 1.7
Hurst's exponent	0.81 \pm 0.05	0.64 \pm 0.07 *
Fractal dimension	1.19 \pm 0.07	1.36 \pm 0.09 *
α_1	1.08 \pm 0.06	0.95 \pm 0.05 *
α_2	1.39 \pm 0.04	1.37 \pm 0.26

* p value < 0.05

Table 1: The clinical and heart rate variables of subjects in the study

traditional measurements, but do give preliminary information on the usefulness of fractal analysis methods in risk stratification of patients with stable CHD.

4 Conclusions

Patients with stable angina pectoris had loss normal fractal characteristics in heart rate variability estimated by non-linear dynamic measures of heart rate behaviour. The measurement of a short-term fractal scaling exponent gives complementary information on abnormal HR behaviour in patients with SAP in relation to other standard measurements. The present study shows that normal fractal properties of RR interval dynamics are altered in patients with SAP. Dynamic analysis of HRV gives independent information that probably cannot be detected by the traditional linear analysis technique. Healthy subjects have a distinct circadian rhythm of HRV, but this rhythm seems to be blunted in coronary heart disease (CHD) patients. Fractal correlation properties and fractal dimension in this study may reflect an altered neuroanatomic interaction that may predispose patients to the development of CHD. Further studies in a larger population will be needed to further define the clinical utility of new

fractal measurements of HRV for risk stratification in patients with CHD.

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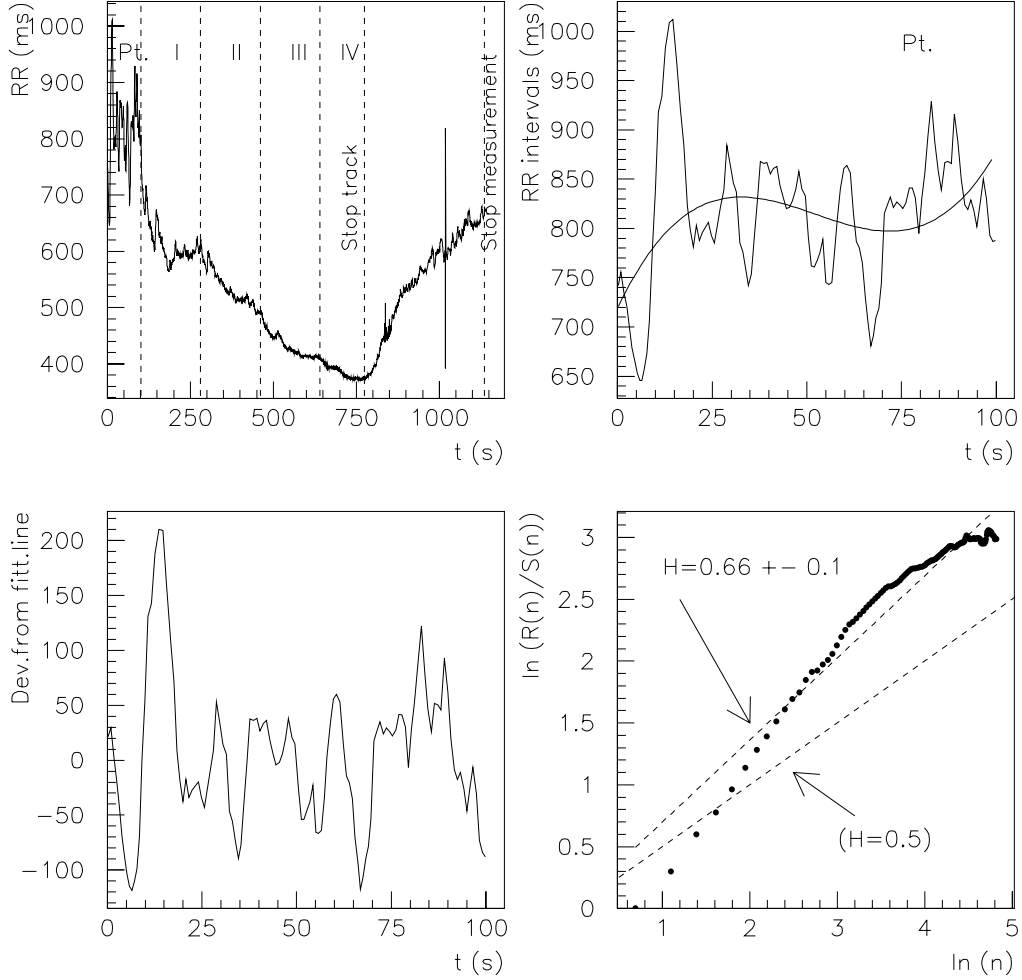


Figure 1: Example of RR intervals in one typical ergometric measurement; RR intervals in unforced regime (pretrigger, Pt.) with a cubic polynomial fit; deviations from the fitting curve; and the R/S calculation result of the Hurst exponent H in comparison with random data, $H=0.5$.

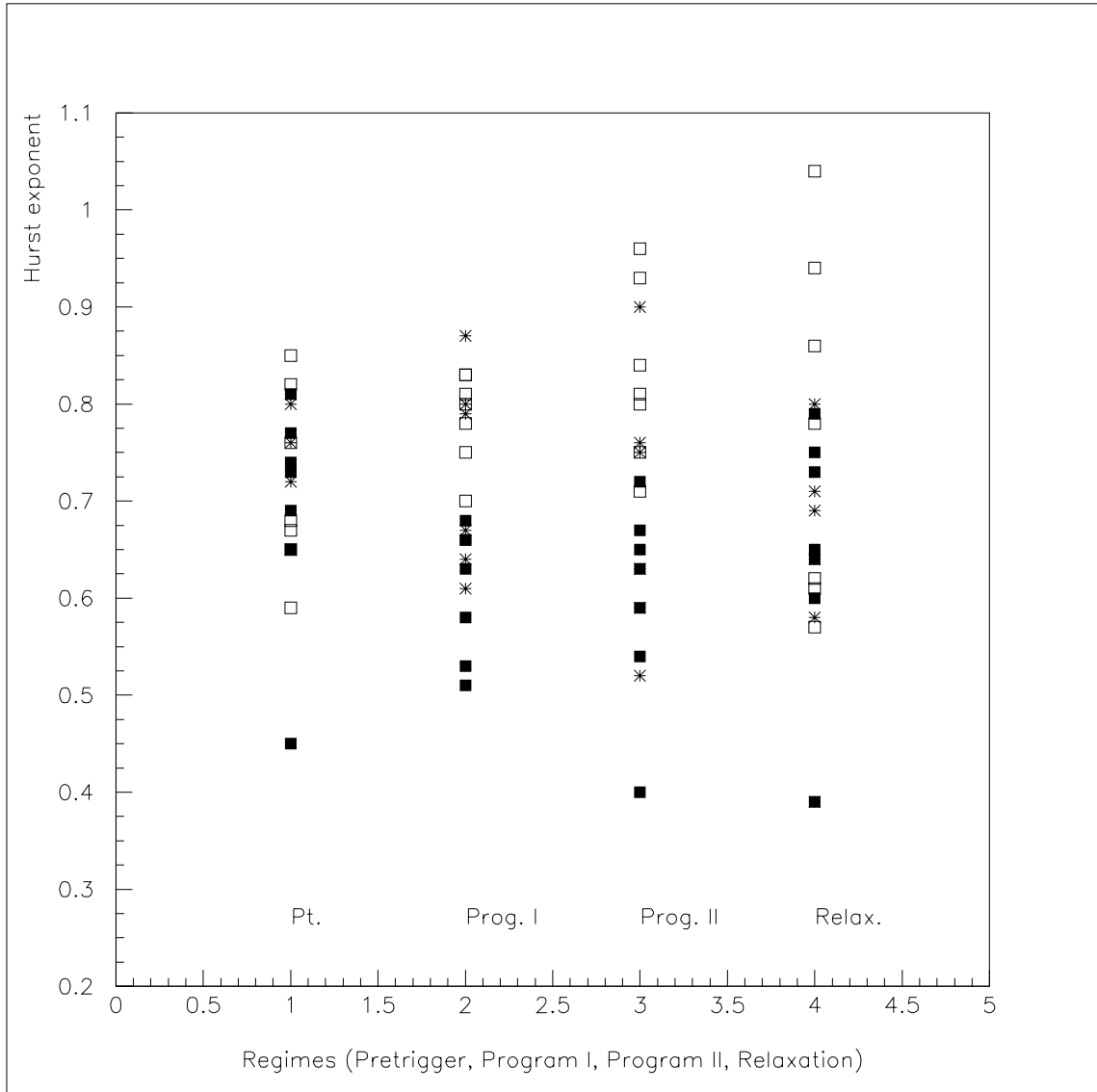


Figure 2: Hurst exponents for different regimes in ergometric measurements; Pretrigger (Pt.), Program I, Program II and Relaxation (30 sec., 3 min., 3 min., 6 min. duration, respectively), with the cubic polynomial fit before the R/S calculation. Open squares correspond to healthy subjects, filled squares to ill subjects and stars to suspected subjects.

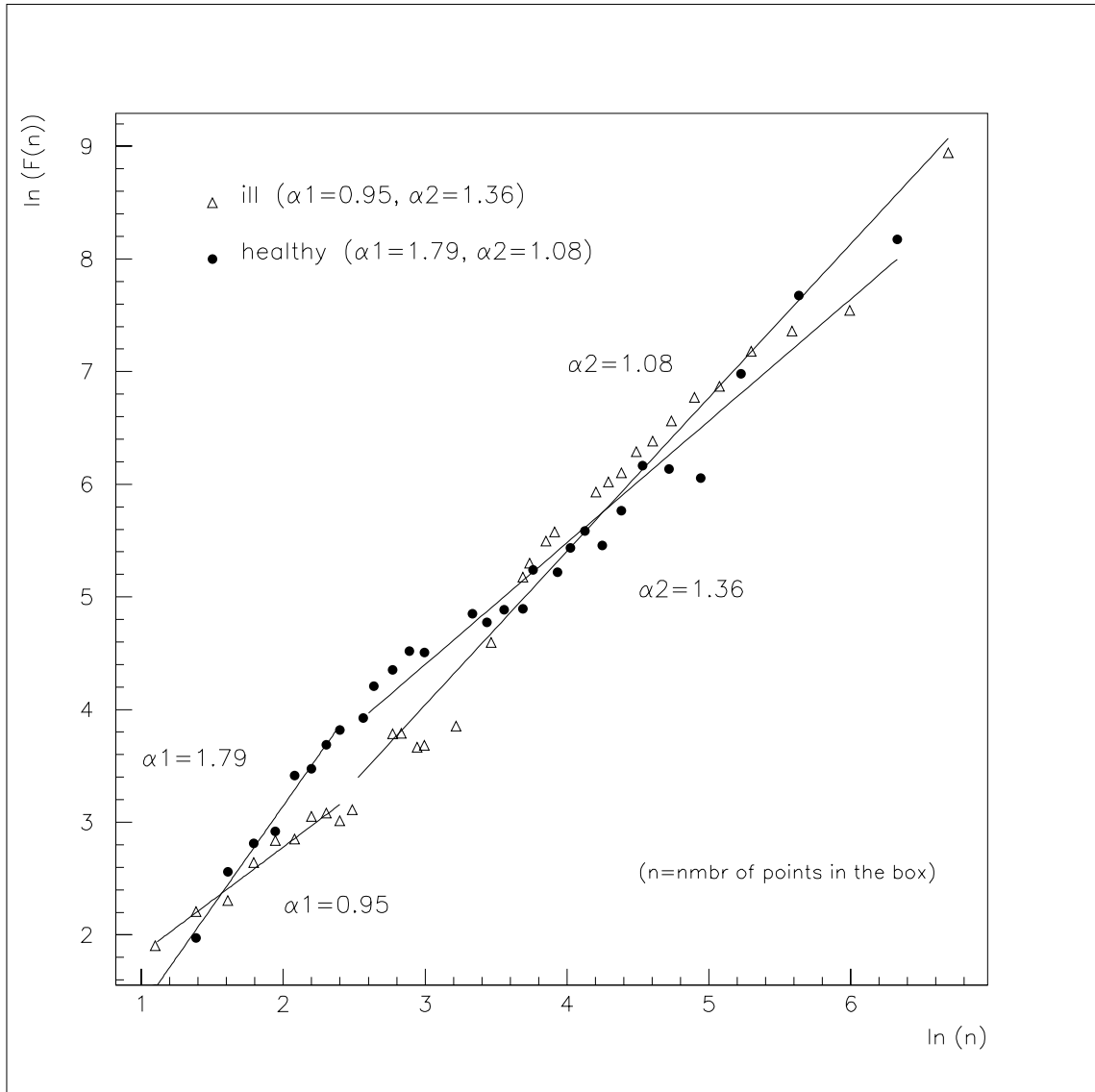


Figure 3: RR intervals analysed using the DFA method showing the difference between healthy and ill (SAP) subjects.